Mucosal Immunity in Primary Immunodeficiencies

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Abstract

The epithelia covering the gastrointestinal, respiratory, urogenital, conjunctiva, and inner ear are integral parts of the immune system. Through mechanical and chemical means, they prevent invasion by pathogens. The mucosal immune system consists of an innate and acquired system that interact with each other in a complex way. The mucosal immune system also has the delicate task of differentiating between pathogens and non-pathogens. The T and B lymphocytes present in the mucous membranes are specific to these sites, differing from those we can find in the peripheral circle, and produce specific responses, such as local IgA secretion. In this chapter, we will discuss in a non-exhaustive way the main components and mechanisms of innate and adaptive mucosal immunity and how this can be compromised in primary immunodeficiencies.

Keywords

T cell development · Mucosal immunity · T helper 1 · T helper 2 · T helper 17 · T regulatory cells · Primary immunodeficiency · Intestinal immunity · Bronchial immunity · Infections · Allergy

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5.1 The MALT

The mucosa-associated lymphoid tissue (MALT) is a secondary lymphoid organ that includes more or less organized lymphoid structures [1]. It includes multiple subregions, the most important being the gut-associated lymphoid tissue (GALT), the nasal-associated lymphoid tissue (NALT), and the bronchus-associated lymphoid tissue (BALT). In the human airway of adults, evidence of an organized lymphoid tissue is still lacking in health, while an induced BALT (iBALT) is present in pathological conditions. The MALT is characterized by region-specific inductive and effector sites. Systemic and mucosal immune systems have distinct functional structures and can be activated and regulated in an independent manner [2, 3]. Common characteristics of the MALT are the presence of different cell types, such as B cells, T cells, dendritic cells (DC), as well as innate immune cells, that together contribute to an efficient immune response. Other common characteristics of the MALT are the lack of afferent lymphatics as well as the presence of high endothelial regions [1, 4, 5].

5.2 Epithelia and Innate Mucosal Immunity in Respiratory Tract and Gut

Mucosal epithelia are constantly exposed to external antigens and, in combination with several cell types, facilitate the protection of the gastrointestinal and respiratory tract [6]. The secretion and composition of saliva, including mucus, secretory immunoglobulin A (SIgA), and humoral innate immune proteins, such as lactoferrin, lysozyme, and the defensins, are regulated by the airway epithelium, which provides a physical and chemical barrier that prevents infections as well as chronic inflammatory processes potentially occurring in response to the constant exposure to antigens. The mucosal epithelium, in combination with localized antigen-presenting cells, has a crucial role in connecting the innate and adaptive immune system via the production of cytokines and chemokines to initiate inflammation in case of infection. However, specialized lymphoid cells and immune mechanisms are present at the mucosal sites to exert an immunosuppressive function on adaptive immune processes to tightly modulate and control inflammatory responses.

L-selectin, a receptor molecule prominent in the head and neck mucosa and in the lymph nodes, regulates the trafficking of lymphocytes to these sites. α-defensins regulate the mucosal immune system of the gut and prevent microbial invasion at the epithelial surface and modulate the activity of different T cell subpopulations for further adaptive responses [7, 8]. Increasing data suggest that at mucosal level, innate immunity is the main regulator of the immune response [9].

Congenital defects in the epithelium can lead to very early-onset IBD [10]. The epithelium has an important regulatory function of innate immunity. Severe colitis was described in two children with biallelic LOF mutation in *ALPI* gene, coding for the intestinal phosphatase alkaline, a brush border metalloenzyme that hydrolyzes phosphate from the lipid A moiety of lipopolysaccharides and thereby drastically reduces Toll-like receptor 4 agonist activity [11].

Mutations in TTC7A, an epithelial protein, can result in various phenotypes that may or may not be associated with combined immunodeficiency (CID), including multiple intestinal atresia (MIA) and very early-onset inflammatory bowel disease [12].

Antimicrobial peptide expression by the intestinal epithelium is believed to have an important function in controlling the number of bacteria around epithelial cells and has recently been suggested to have a principal role in the pathogenesis of inflammatory bowel disease. An important role in the regulation of antimicrobial peptide expression is played by the NF-κB signaling pathway [13].

A role of lack of defensins was suggested in the development of colitis in NEMO hypomorphic mutation. In $NEMO^{IEC\text{-}KO}$ mice, the expression of beta-defensin-3 (homologous to human beta-defensin-2, which predisposes to colonic Crohn's disease in humans) [14] was significantly downregulated [15].

5.3 Mucosal T Cells

Conventional T cells develop in the thymus from double-negative (CD4−CD8−) progenitors. After TCRβ expression, CD4−CD8− cells enter a double-positive (CD4+CD8+) stage. The strongly self-reactive cells are eliminated by negative selection, while T cells that present low affinity to self-antigens develop into single-positive CD4+ (via interaction with MHC II) and single-positive CD8+ (by interaction with MHC I) [16].

After leaving the thymus, naïve CD4+ T and CD8αβ+ T cells migrate through the circulation to the gut-associated lymphoid tissues (GALTs), such as the mesenteric lymph nodes and Peyer's patches. Here, they are primed by the antigen-presenting cells (APCs) and by the upregulation of gut-homing molecules, such as CCR9, CD44, integrin α4β7, LFA-1, and VLA-4, that are able to home to different mucosal sites guided by the presence of their specific ligands. The APCs and the intestinal epithelial cells (IEC) regulate differentiation of CD4+ T cells into Th1, Th2, Th17, and intestinal Treg (iTreg) in response to the various food or microbial antigens present at the site [17]. This intestinal T cells mainly migrate to the lamina propria and present an effector memory phenotype.

One small population of thymocytes does not undergo the selection in the thymus, lacks the so-called "conventional" T cell coreceptors (CD4 and CD8αβ), and expresses either TCRγδ or TCRαβ and CD8αα homodimers and are called unconventional T cells. These cells mainly exert regulatory functions and are mainly located between the gut lumen and enterocytes as intraepithelial lymphocytes (IELs) [18–21].

γδ T cell were also described in the lung during respiratory infections, where they contribute to clearance of intracellular and extracellular bacteria. During active pulmonary tuberculosis circulating, γδ T cells are an important source of IL17 [22, 23].

Conventional and nonconventional T cells both concur to provide protection against pathogens and, at the same time, to maintain immune tolerance to commensals and antigens derived by food, contributing to intestinal homeostasis.

IELs play an important role in maintaining the barrier function. A homeostasis in the gut mucosa is depending from a balance between T cells with effector function, which rapidly mount an immune response against pathogens, and regulatory T cells, as well as IL-10-producing CD4+ T cells. A disbalance between these specialized players of the adaptive immune system can lead to autoimmune enteropathy.

IEL were also described in the lung. In biopsies from healthy volunteers, 20 bronchial IEL/100 epithelial cell nuclei were found, mostly expressing ab T cell receptors [24].

Intestinal tolerance to commensal microorganisms and food is mainly mediated by FOXP3+ Treg cells. From the total of CD4+ T cells in the intestine, around 30% are localized in the colon and approximately 20% of those in the small intestine. Gut microbiota affect the number and function of Treg cells. In a mouse model, the number of Treg cells in the small intestine was found to be significantly reduced in germ-free mice, suggesting that a microbiota-independent induction occurs in the small intestine, but not in the colon [25].

Also, the airway mucosa contains specialized lymphoid cells able to regulate and modulate inflammatory responses. It was shown that inducible Tregs ($foxp3^{+}helios^{-}$) in the airways contained the highest frequency of IL-17-producing cells of the $CD4^{+}$ T cell subsets. A higher percentage of $foxp3^{-}CD4^{+}$ T cells produced IL-10 than peripheral blood [26]. The higher frequency of inducible Treg-producing IL-17 may be important for the transport of SIgA, through the induction of T-helper (Th) 17 cells required for T cell-dependent immunoglobulin A production as shown in Peyer's patches [27].

Other T cell subsets considered as nonconventional T cells are MAIT cells. When these nonconventional cells emerge from the thymus, they are already able to act as effector cells. Their TCR are anyway not able to recognize a wide variety of antigens. These characteristics suggest for these cells a role between innate and adaptive immune system.

MAIT cells are found in mucosal tissues, like the intestine and the lung as well as in the liver. These cells can recognize only conserved nonpeptide antigens presented by the MHC class I-like protein MR1 and when activated produce TNF-a and IFN-g, controlling bacterial intracellular infections. These cells are present in the lung and seem to be an important role in respiratory infections. Circulating MAITS were reduced in patients with tuberculosis and almost absent in patients with active tuberculosis, probably due to their recruitment in the lung. Here, they were shown, in murine models of respiratory bacterial infections, to expand and produce IFN-g, TNF-a, and IL-17. Mice lacking MAIT cells showed reduced and delayed response to BCG and *F. tularensis* infection [28, 29]. MAIT cell alterations were recently found in CVID patients that resulted reduced in number and frequency [30]. The remaining cells expressed activation markers and as well as a reduced IFN-g response when challenged in vitro with *E. coli*, similarly to patients affected by

chronic infections, like HIV HTLV1 and HCV [31–34], and to patients with cystic fibrosis [35]. Lower blood MAIT cells were also observed in patients with chronic *H. pylori* or mycobacterial infections [36, 37] (Fig. 5.1).

5.3.1 Autoimmune Enteropathy, Regulatory T Cells, and IL-17 Production

Autoimmune enteropathy (AIE) is a rare disease, clinically manifesting with chronic diarrhea, and malabsorption, that can be associated with autoimmune comorbidities [38].

A disbalance between Tregs and effector T cell activation is one important factor in the development of AIE.

Patients with immune dysregulation polyendocrinopathy enteropathy X-linked syndrome (IPEX), an X-linked disease caused by mutations in FOXP3, typically present with AIE. The role of Foxp3 is crucial for the development and function of regulatory T cells (CD4+CD25+) [39]. Non-IPEX adult-onset cases have been also reported [40]. FOXP3 expression, as well as CD4+CD25+ Treg expression, is reduced in IPEX, which may explain the intestinal inflammation and villous atrophy due to uncontrolled activation of gut-associated lymphoid tissue. Biopsies from the duodenal mucosa in these patients showed CD4+CD8+ T cell infiltrates [41].

A phenotypic and functional analysis in a severe case of AIE in a non-IPEX adult patient demonstrated production of IFN-γ and IL-17 by intraepithelial T lymphocytes (IEL) in the duodenal mucosa. These findings were absent in samples from Crohn's and celiac disease or healthy controls. In this study, it was shown that TCR-activated IL-17 production has different cytokine and transforming growth factor-β (TGF-β) requirement in the lamina propria and intraepithelial CD4+ and CD8+ lymphocytes. TGF-β in its active form was found in the intestinal mucosa of AIE patients. Tregs with low expression of FOXP3 maintain the ability to produce TGF-β and increase IL-17 production by IEL CD8+ T cells [42]. Remarkably, it was shown in mice models that Treg cells are able to suppress $CD8\alpha^+$ T cell receptor (TCR)$\gamma\delta^+$ T cells, including an interleukin-17 (IL-17)-expressing population, responsible for inflammatory colitis [43].

Regulatory T cell defects are at the basis of gastrointestinal involvement in immune dysregulation syndromes. Gastrointestinal involvement in IPEX syndrome, CD25 deficiency, and CTLA4 insufficiency is described in Chap. 15 of this volume. LRBA deficiency is discussed in the second book of this series, Humoral Primary Immunodeficiencies [1].

Increased and uncontrolled function of effector T cell can as well lead to inflammatory entheropathy.

A disbalance in Treg/ effector T cell activation is at the basis of autoimmune entheropathy in other complex immune deficiencies, like MALT1 deficiency and DOCK 8 deficiency, where a reduced activity of Tregs was described, as well as in STAT1 GOF [44] and STAT3 GOF mutations [45] and in the recently described JAK1 GOF [46].

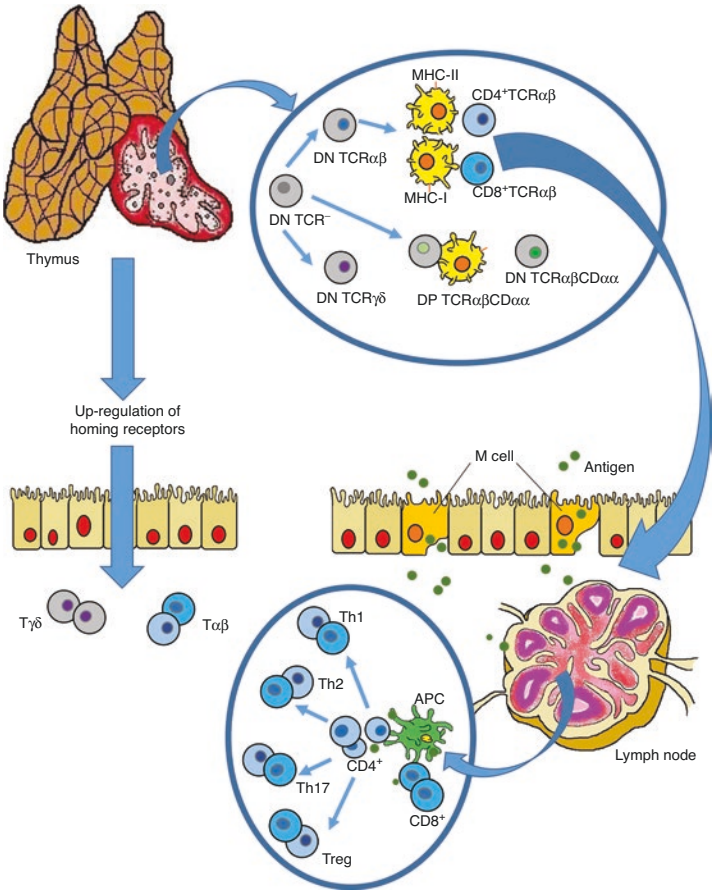

Fig. 5.1 *Origin and development of T lymphocyte lineage subsets.* Conventional T cells develop in the thymus from double-negative (DN) (CD4−CD8−) progenitors. After TCRαβ expression, CD4−CD8− cells enter a double-positive (DP) (CD4+CD8+) stage. The strongly self-reactive cells are eliminated by negative selection, while T cells that present low affinity to self-antigens develop into single-positive CD4+ (via interaction with MHC II) and single-positive CD8+ (by interaction with MHC I). After leaving the thymus, naïve CD4+αβ+ T and CD8+αβ+ T cells migrate through the circulation to the gut-associated lymphoid tissues, such as the mesenteric lymph nodes and Peyer's patches. Here, they are primed by antigen-presenting cells (APCs) and by upregulation of gut-homing molecules, such as CCR9, CD44, integrin α4β7, LFA-1, and VLA-4, that are able to home to different mucosal sites guided by the presence of their specific ligands. The APCs and the intestinal epithelial cells (IEC) regulate differentiation of CD4+ T cells into Th1-producing IFN-γ, Th2-producing IL-4, Th17-producing IL-17, and intestinal T regulatory cells (Treg) in response to the various microbial or food antigens present at the site. These mucosal T cells mainly migrate to the lamina propria and present an effector memory phenotype. One small population of thymocytes does not undergo the selection in the thymus, lacks the so-called "conventional" T cell coreceptors (CD4 and CD8αβ) and express either TCRγδ or TCRαβ and CD8αα homodimers and are called unconventional T cells. These cells mainly exert regulatory functions and are mainly located between the gut lumen and enterocytes as intraepithelial lymphocytes. Υδ+T cells have been also described in the lung during respiratory infections, where they contribute to clearance of intracellular and extracellular bacteria. Conventional and nonconventional T cells both concur to provide protection against pathogens and, at the same time, to maintain immune tolerance to commensals and antigens derived by food, contributing to intestinal homeostasis

5.3.2 CD4+ T Cell Depletion in Gut Mucosal and Chronic Granulomatous Disease

Chronic granulomatous disease (CGD) is an inherited primary immunodeficiency affecting phagocytes. Patients affected by this condition harbor mutations in NADPH oxidase, leading to impaired reactive oxygen species (ROS) production by neutrophils and monocytes, defects in microorganism clearance, and chronic inflammation [47, 48]. T cell alterations have been previously reported [49]. The underlying mechanisms related to the T cell compartment alterations remain unclear and need further investigation.

Progressive CD4+ lymphopenia, with reduction of naive cells, lymphocyte activation, and expansion of interleukin (IL)-17-producing CD4 T cells, was shown in an adult CGD patient. At the age of 34, the patient presented persistent diarrhea with watery stool, without blood or mucous, associated to hypoalbuminemia without a microbial cause or malabsorption being identified. An endoscopy with biopsies was performed. Lymphoid aggregates and inflammatory infiltrates were reported. Cell suspensions from sigmoid biopsies were analyzed by flow cytometry, showing reduced number of CD4+ T cells, compared to control at the intestinal mucosa level (with decreased CD4+/CD8+ ratio) [50].

The pathogenesis of T cell alterations in the mucosal compartment seems to be related to immunosenescence and needs further investigation.

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